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REMARKS

Claims 1-10 and 15-18 have been canceled as being directed to non-elected subject matter. Claim 11 has been amended to more clearly define that which applicants believe to be their invention. More particularly, applicants have amended claim 11 to specify that the vaccine is formulated as an aqueous solution/suspension, i.e., the pharmaceutically acceptable carrier consists of water or an aqueous physiological solution.

Claims 11-14 stand rejected under 35 USC 103 as being unpatentable over Kedar et al, in view of Haan et al and Knight et al. Applicants respectfully traverse this rejection.

Applicants have found that contrary to the general teaching at the time of this invention, an aqueous vaccine formulation could be produced for influenza virus that was highly efficacious. At the time of the invention those skilled in the art understood that to obtain a strong immunogenic response vaccine formulations needed to be oil based. Consistent with this general teaching, each of the three references cited by the Examiner (Kedar et al, Haan et al and Knight et al) each disclose oil-based vaccine formulations.

As noted by the Examiner, Kedar et al. (1999) teach the preparation of a vaccine wherein an antigen is first dissolved in an aqueous solution. However, the preparation of the antigen solution is simply an initial processing step used to prepare the final vaccine formulation. The completed vaccine formulations as taught by Kedar et al for administration to patients are liposome based formulations. When preparing a liposomal formulation, it is a natural procedure to prepare an aqueous solution first, when the antigen is water soluble. This aqueous core is then encapsulated in the liposome delivery vehicle. Accordingly, Kedar teaches administering a vaccine composition that has a large lipid content. Thus applicants respectfully submit that while a vaccine solution is initially prepared, the final vaccine composition is not administered as an aqueous solution, but rather as a liposomal formulation.

Similarly, the secondary de Haan et al. (1995) reference is also limited to the administration of liposomal compositions. de Haan et al teach that secretory IgA is produced by intranasal administration of a liposomal formulation of influenza antigen, and report the induction of a mucosal immune response by intranasal administration of multilamellar vesicle (MLV)–type liposomal formulation of HA antigen. Although liposomes incorporating HA were made via dissolution of the antigenic formulation into PBS, the formulation used has HA incorporated in closed vesicles that consist of a lipid bilayer and possess an internal aqueous layer (i.e., liposomes). Consequently, the antigen exhibits the behavior of a lipid, and not of a solution.

Knight et al. (1977) also fails to teach or suggest a vaccine composition wherein the carrier consists of water or an aqueous physiological solution. Knight et al report the injection (administration) of PolyIC, and study the adjuvant effect by using an oil-base formulation of a fowl Newcastle disease vaccine and dsRNA, and suggest PolyICs effectiveness as an adjuvant. Use of an aqueous formulation is negated in this publication. In addition, the influenza virus and the Newcastle disease virus are completely different viruses that belong respectively to *Orthomyxoviridae* and *Paramyxoviridae*. One of ordinary skill in the art would judge at the point of time of the publication of Knight et al., that both antigen and dsRNA should be prepared as an oil-base formulation, and particularly from the virus challenge test of Table 4 of Knight et al, that the vaccine will have no effect when it is administered as an aqueous formulation. From the publication of de Haan et al. one would determine that secretory IgA will be produced when antigen is encapsulated in a liposome (which shows a delivery behavior of oil) and administered intranasally. From Knight et al. one would deem that antigen and adjuvant must not be prepared as a solution, but must be encapsulated in a liposome.

Liposomes (lipid vesicle) are essentially an artificial lipid membrane. They are typically prepared by suspending a phospholipid into 50% (weight ratio) or more water at or above the gel-liquid crystal phase transition temperature which is specific to the phospholipid. The resulting closed vesicle consists of a lipid bilayer and possesses an internal aqueous layer.

Consequently, although the Examiner asserts that Kedar et al. teach "administration of influenza antigen in a solution", applicants respectfully submit that Kedar et al. merely disclose preparation of a "liposomal formulation in which vaccine antigen and cytokine are combined together, for providing cell-mediated immunity over a long period of time after administration". Preparing a liposomal formulation confers an oily (lipophilic) behavior to the vaccine composition *in vivo*, and thus the vaccine composition cannot be characterized as being aqueous, nor will the composition have an aqueous behavior in any way. In fact, the compositions of Kedar and Haan are emulsions. Emulsions that are produced from water and oil (for example, water-in-oil type emulsion, oil-in-water type emulsion, water-in-oil-in-water type emulsion) may be used as adjuvants in vaccines. Water-in-oil type emulsions are generally used as adjuvants in animal vaccines (for example, poultry vaccines). Generally, in order to produce water-in-oil type emulsions, aqueous phase antigen is added gradually to a mineral oil carrier or the like in the presence of one or more emulsifying agents to produce micelles composed of oil drops, and the aqueous antigen comes to exist within these oil drops. This oil composition induces the transition of immune cells to the site of injection to defend against antigens, and it is believed that it also

acts to extend the time for the immune cells to treat the antigens. Compared to injecting the above-mentioned antigen alone, the addition of the oil provides an enhancement of the above-mentioned immune response.

At the time of the present invention, those skilled in the art were aware that when an aqueous formulation and oil-base formulation of an antigen other than the influenza virus (ND) were compared, (even when using dsRNA as an adjuvant), acceptable efficacy was only obtained with oil-based formulations. This is presumably the reason the cited prior art references all utilize oil-based formulations. In 1995, at the point of time of de Haan et al., the effectiveness of the influenza HA antigen that was encapsulated within a liposome capsule was demonstrated, and in 1999, at the point of time of Kedar et al., the combination of an antigen and an adjuvant (other than dsRNA) were demonstrated to be better off when encapsulated within a liposome capsule.

Consequently, from the above-mentioned cited references, one of ordinary skill in the art would deem that influenza antigen and adjuvant candidate would need to be in a water-in-oil type liposomal formulation, and would not conceive of the constitution of the claimed invention. The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). Thus when the teachings of Kedar et al, Haan et al and Knight et al are considered for all their combined teachings, the references still fail to teach or suggest the present invention which uses a unique combination of double-stranded RNA and a subunit antigen or inactivated antigen of an influenza virus suspended in an aqueous carrier.

Furthermore, applicants have discovered their unique aqueous vaccine formulations have surprising efficacy when administered intranasally. In particular, the intranasally administered aqueous formulations of double stranded RNA and an influenza virus antigen produce the following effects:

(1) virus specific IgA is efficiently induced on the mucosal surface (Example 1 and Fig. 1),

(2) lethal infection is prevented in a virus challenge test using mouse (Example 1, Fig. 2 and Table 1),

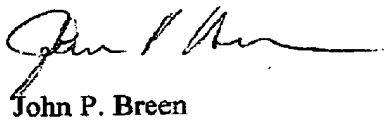
(3) the vaccine is effective in a virus challenge test of a different strain (cross-prevention ability) (Example 2, Figs. 3 and 4), and

(4) even by intranasal inoculation, side effects on the central nerve system are unexpectedly absent and safety requirement is satisfied as well (Example 3 and Fig. 5).

Accordingly, applicants respectfully submit the cited references fail to teach or suggest applicants' use of the unique compositions as claimed in the amended claim set. Therefore, applicants respectfully request the withdrawal of the rejection of claims 11-14 under 35 USC 103 as being unpatentable over Kedar et al, in view of Haan et al and Knight et al.

Applicants respectfully request allowance of the claims, and passage of the application to issuance. If any further discussion of this matter would speed prosecution of this application, the Examiner is invited to call the undersigned at (434) 220-2866.

Respectfully submitted,



John P. Breen
Registration No. 38,833
Attorney for Applicants

(317) 261-7940
Indianapolis, Indiana 46204